

THE NATIONAL INSTITUTES OF HEALTH

FY 2000 INVESTMENTS

Improving the Nation's Health Through

Medical Research

on

Prevention, Diagnosis, and Treatment

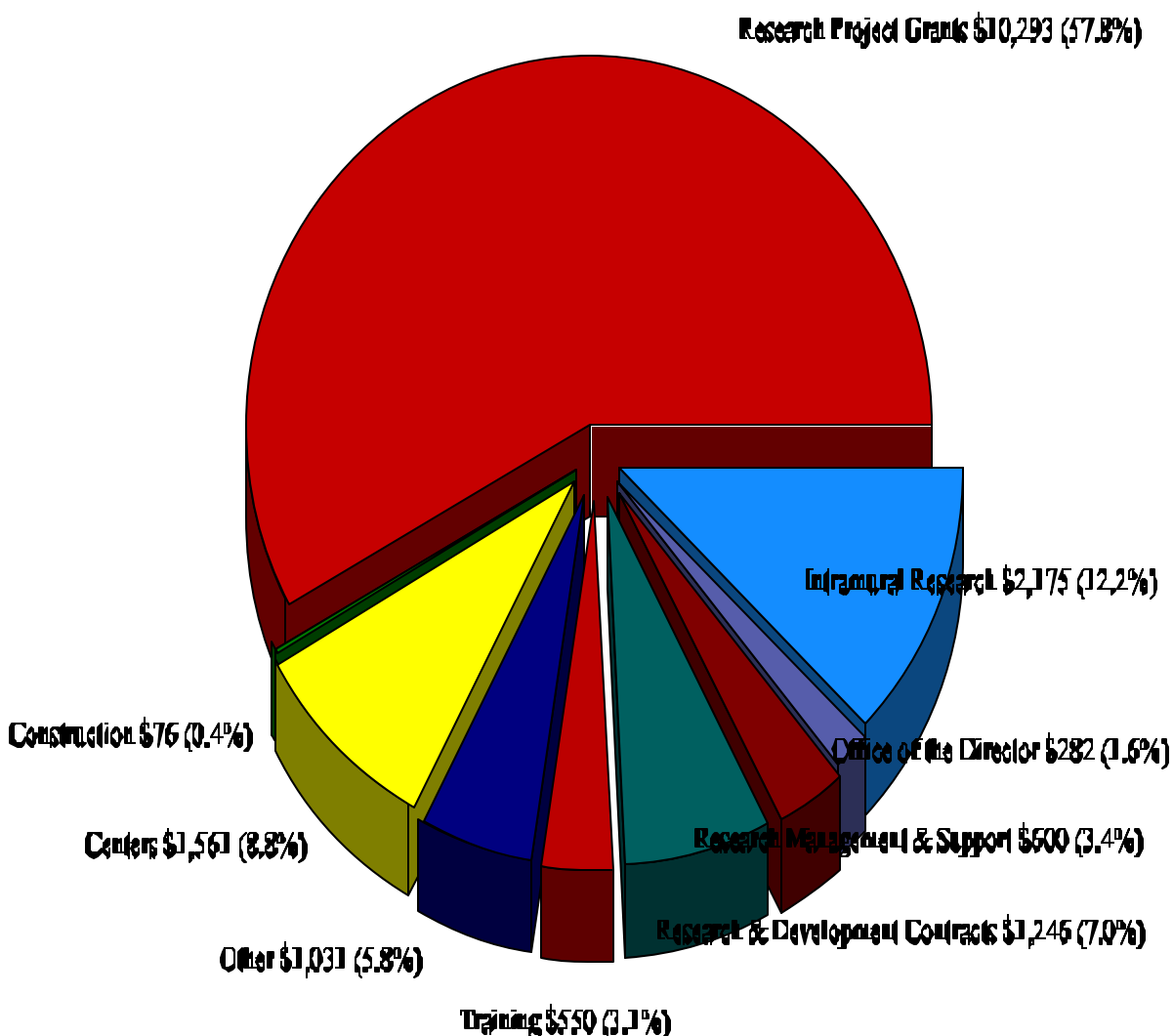
National Institutes of Health
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Table of Contents

Chart: FY 2000 NIH Budget by Mechanism	i
Chart: FY 2000 NIH Increase by Mechanism	ii
What is the NIH and how is it organized?	1
What is the role of the NIH in improving the prevention, diagnosis, and treatment of disease and disability?	2
How does the NIH fund research?	4
How is the NIH spending the FY 2000 budget increase?	5
Research Project Grants	6
Centers	13
Other Research Programs	15
Research Training	20
Research and Development Contracts	21
Intramural Research	25
Research Management and Support	29
Construction	30
Office of the Director Activities	31

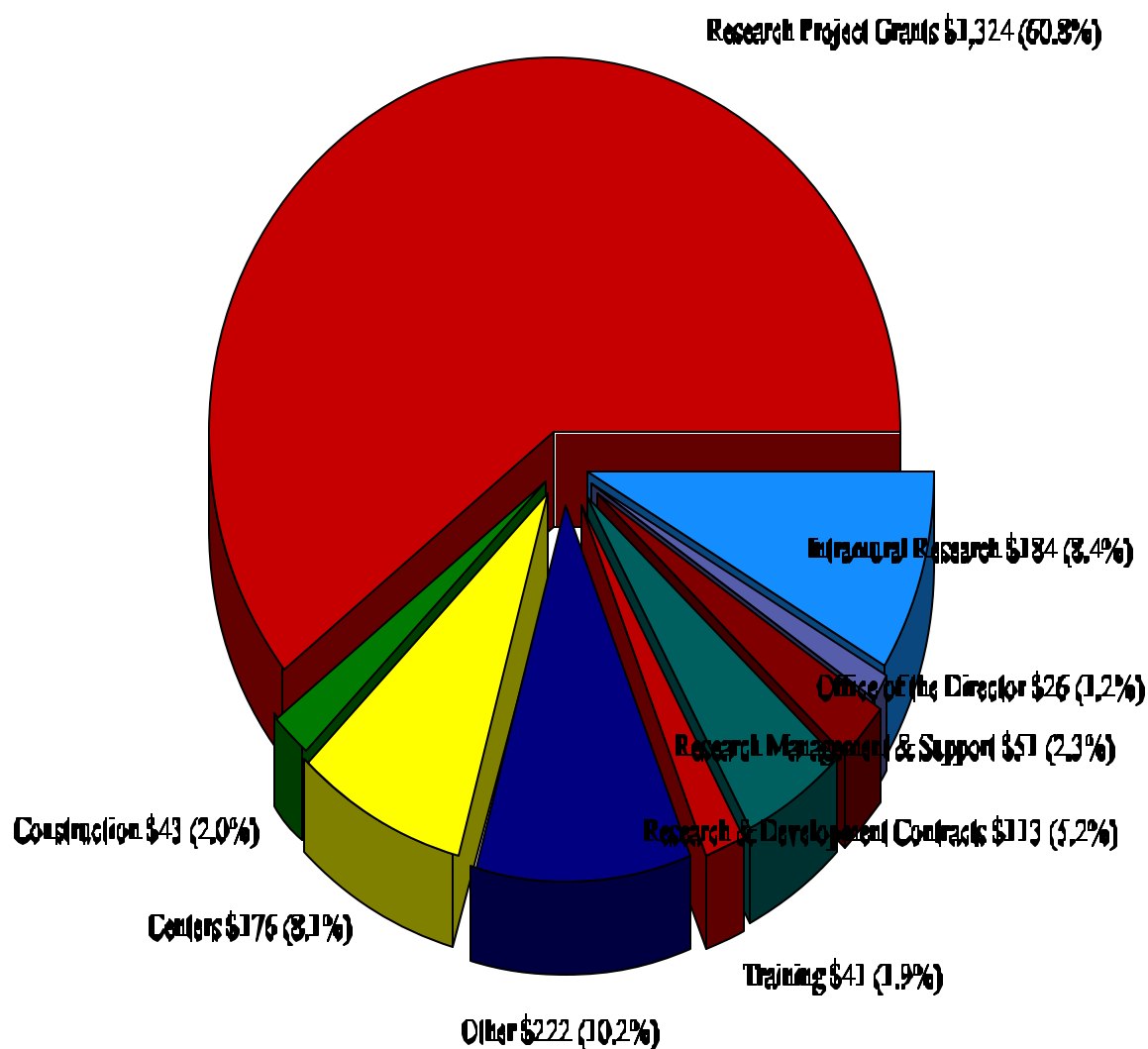
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FY 2000 Total = \$17,813 million



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FY 2000 Total NIH Increase = \$2,180 million



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OVERVIEW

What is the NIH and how is it organized?

Began as a one-room Laboratory of Hygiene in 1887, the National Institutes of Health (NIH) today is one of the world's foremost medical research centers, and the Federal focal point for medical research in the United States. The NIH is one of eight health agencies of the Public Health Service which, in turn, is part of the U.S. Department of Health and Human Services. Comprised of 24 separate Institutes and Centers, NIH has 75 buildings on more than 300 acres in Bethesda, MD. From a total of about \$300 in 1887, the NIH budget has grown to \$17.8 billion in 2000.

The NIH mission is to uncover new knowledge that will lead to better health for everyone. NIH works toward that mission by: conducting research in its own laboratories; supporting the research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helping in the training of research investigators; and ensuring the availability of the physical infrastructure that enables the remarkable successes of the medical research enterprise. The Nation's investment in NIH research has resulted in development of critical knowledge and has led to far-reaching improvements in health, health care, and the quality of life. These improvements have profoundly affected our primary concerns regarding disease prevention, treatment and quality of life.

The activities of the NIH Institutes and Centers (ICs) range from basic research that explores the fundamental workings of biological systems and behavior, to studies that examine disease and treatments in clinical settings, to prevention and to population-based analyses of health status and needs. The NIH that is known to most Americans encompasses the research institutes focused on diseases (e.g., cancer, diabetes), primary organ systems (e.g., heart, eye, kidney), or a stage of life (e.g., children, the aging). Yet, no less essential to the Nation's health are NIH programs that address overarching scientific needs and opportunities. Included here are such efforts as deciphering the human genome, understanding cellular and tissue biology and physiology, training investigators in relevant scientific fields, and developing the array of technologies dictated by the needs of cutting-edge research.

NIH's mission to advance medical knowledge and sustain the Nation's medical research capacity is accomplished by sustained Federal stewardship. NIH relies on several fundamental principles in planning and managing its programs and resources. These principles are: provide scientific leadership and establish research priorities, fund the best research, conduct leading-edge research in NIH laboratories, disseminate scientific results and research-based health information, facilitate the development of health-related

products through technology transfer, ensure a continuing supply of well-trained laboratory and clinical investigators, and sustain the Nation's research facilities.

What is the role of the NIH in improving the prevention, diagnosis, and treatment of disease and disability?

In the last century, the scientific community, both public and private, worked collaboratively to prevent or treat once deadly infectious diseases that are now given no more thought than the common cold. Examples of the astounding medical breakthroughs that followed our increased understanding of medical science include: the development of antibiotics and organ transplantation, life-extending and life-saving cancer therapies, the identification of the AIDS virus and the drugs to treat AIDS, and discoveries involving the chemicals in the brain that are important in drug addiction and mental illness.

As we begin a new century, medical science stands on the threshold of research advances that were once inconceivable. We have identified the genes responsible for a large number of our normal functions and the genetic abnormalities that cause many diseases, such as Huntington's disease, cystic fibrosis, and certain forms of deafness.

Our goals are simple: to develop new knowledge about normal and abnormal biological functions and behavior; to develop new or improved instruments and technologies for use in research and medicine; to develop new or improved approaches for preventing or delaying the onset or progression of disease and disability; to develop new or improved methods for diagnosing disease and disability, and to develop new or improved approaches for treating disease and disability. These goals are met through support of three mission-related activities: research, research training and career development, and research facilities. NIH supports and conducts a broad range of research, including basic, translational, and clinical research; population-based studies; behavioral research; and health services research. In addition, the timely dissemination of medical and scientific information is a key activity. NIH's research training and career development activities address the need for a steady supply of creative and well-trained personnel to conduct medical research. The primary goal of NIH's programs in graduate training and career development is to recruit, train, foster, and retain highly-trained investigators who are likely to perform research that will benefit the Nation's health. Finally, NIH's support of research facilities ensures that the scientists have modern, efficient, and safe facilities in which to conduct their work.

Although the word "science" comes from the Latin *scientia* meaning "known things," scientists and the practice of science exist because of what we do not know. The aim of science is to move the unknown into the realm of the known and then, with a greater store of knowledge, begin again, as if advancing a frontier. This basic truth about science makes it different from other enterprises. Science deploys its resources and talents to explore new areas and produce fresh results, which are not endlessly replicated, but that pave the way for future and different explorations. The many disciplines of medical research contribute to the store of knowledge and to one another, and all deserve exploration and funding. Discoveries that will increase our knowledge of the causes, progression, and treatment of cancer, for example, may stem from epidemiological, clinical, and molecular research conducted by teams of investigators building on the discoveries of their predecessors, including those in other fields. While the road is paved by arcane research, the outcome - better diagnosis, prevention and treatment - is simply understood.

Since it is impossible to know with certainty which area will produce the next important discovery, the community of science, of which the NIH is a part, has to be open to all ideas. No one field has all the answers, but investigators in many different fields can ask the questions that will provide more knowledge about disease and health. It is a striking characteristic of science that it requires both creativity and precision to generate ideas and results. The precision with which investigators pursue an idea, however, cannot alter the inescapable truth that many of the results of research are unpredictable, given the pursuit of unknown things. It requires a special kind of “scientific open mindedness” to analyze results and not simply conclude that an experiment failed because it did not yield an answer to the original question, but rather to recognize the potential implications of an unanticipated finding for other important biological questions. For example, the investigator examining patients with ataxia telangiectasia, a rare genetic disease, who discovers something new about the origins of cancer has not “stumbled” on a discovery, but rather has put himself or herself in a position to make the discovery, to recognize its unexpected significance, and to bring it into the realm of known things which would not have happened otherwise.

Although much of NIH funding supports research projects that are of obvious relevance to specific diseases and public health, it also places a high priority on fundamental, untargeted research. Initially, and sometimes for many years, it is unclear what role this research may play in improving health, but history has shown many times over that a basic research finding might prove to be a critical turning point in a long chain of discoveries leading to improved health. Basic research programs can be evaluated meaningfully on a regular basis, but ultimate outcomes of research into fundamental processes are seldom predictable or quantifiable in advance.

This unpredictability has three important implications. First, science is by nature structured and self-correcting, so that either a predicted or an unforeseen discovery has the advantage of adding to basic scientific knowledge and giving new direction to further inquiries. This self-correction, carried out under public scrutiny of the results, means that science operates in a dynamic environment. The self-correcting nature of scientific inquiry requires a multiplicity of investigative approaches and the ability to adapt quickly to change. Importantly, because the system is inherently self-correcting, “bad ideas” do not get a second chance. On the other hand, failure is allowed. Science could not proceed otherwise.

Second, science and its administrators must constantly reevaluate and often change their priorities in light of new discoveries. Very simply, science itself sets its priorities as it refreshes and enlarges knowledge: the more that is known the better are the next set of questions to be asked. Thus, while goals may not change, the route to fulfilling them might well be amended along the way. It is by asking as many questions as can be formulated and by prudently spending resources that the most promising medical priorities can be pursued. As priorities shift and acquire sharper focus, scientists are better able to look across the spectrum of biological and biomedical disciplines and of diseases. Constantly renewed knowledge enables scientists to examine, for example, the effects of pesticides not on one kind of cancer but on all cancers. Moreover, the answers to fundamental questions such as “what turns genes on or off?” will lay the groundwork for targeting the diagnosis and treatment of chronic diseases such as Alzheimer’s disease, cancer, and diabetes.

Third, tracking the many aspects of fundamental science is a daunting challenge that must capture quantitative, qualitative, and institutional dimensions. History shows us that basic research often leads to outcomes that were unexpected or took many years or even decades to emerge. Thus measures of the practical outcomes of basic research usually must be retrospective and historical. It is normal and necessary for basic research investigators to modify their goals, change course, and test competing

hypotheses as they move closer to the fundamental understandings that justify public investment in their work. Therefore, it is necessary to evaluate the performance of basic research programs by using measures not of practical outcomes but of performance, such as the generation of new knowledge, the quality of the research performed, and the attainment of leadership in the field.

By supporting disease-related and basic research projects using a variety of mechanisms, described in more detail below, the NIH can achieve both near-term improvements in the diagnosis, treatment, and prevention of specific diseases as well as long-term discoveries in basic science that in time will produce great advances in our ability to understand, treat, and prevent disease or delay its onset. The challenge is to devise assessment strategies appropriate to the creative processes of science and innovation.

How does the NIH fund research?

Most of the NIH's budget supports the individual research projects conceived of and conducted by either government scientists working on the NIH campus or scientists based elsewhere, at universities, medical, dental, nursing, and pharmacy schools, schools of public health, non-profit research foundations, and private research laboratories. These scientists have been trained in one or more disciplines of science and are committed to enhancing knowledge related to human health and disease through research. NIH support of these research projects includes the salaries of scientists and technicians and the cost of equipment such as lasers or computers; of supplies such as chemicals and test tubes; and of procedures conducted with research patients.

Funding medical research also includes paying the costs associated with research, such as maintenance of buildings, electricity and library services, care of laboratory animals, and salaries of administrative staff who, for example, handle the financial aspects of the grants and set up review panels to ensure that patients participating in research are adequately protected. This is true for all research, whether conducted in the intramural program by government scientists or through the extramural program by scientists in universities and medical schools or by scientists working in industry.

An imperative of supporting medical research is making a commitment to scientists to fund their work for a period of time sufficient for the projects to produce results. Research takes time. NIH grants are awarded for an average of four years; therefore, the bulk of each Institute's annual budget is already committed to funding the remaining years of research projects. The need to continue funding projects over multiple years is an important criterion when deciding to fund new projects. Accordingly, in any given year, only about 25 percent of the total funds allocated for research projects is available to fund new projects that may change the course of a line of research or move research into an entirely new area.

Finally, NIH also must devote funds to ensuring that NIH-supported scientists have adequate facilities in which to conduct their work. Many of the advances in medical research that are leading to more effective treatments for illnesses reflect stunning innovations in sophisticated, but often costly, research technologies that are far beyond the capacity of all but a handful of institutions to purchase, construct, or maintain. Ensuring broad access to these research resources creates efficiencies that make the research dollar go farther, while providing critical resources to all scientists.

Through the support of these activities, NIH has had remarkable success in furthering the understanding of human biology and in developing new treatments, diagnostics, and preventive strategies. Ensuring NIH's record of scientific achievements will require continued strong and stable support for medical research.

FY 2000 PLANS

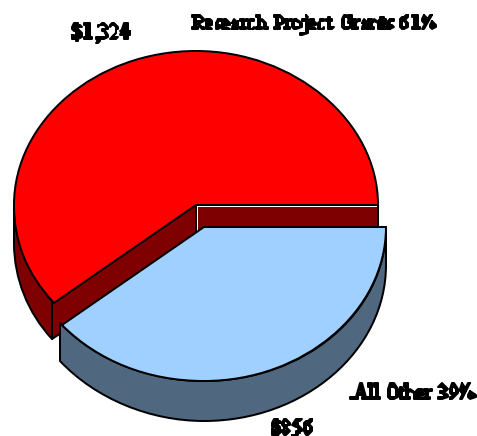
How is the NIH spending the FY 2000 budget increase?

The dramatic increases in the NIH budget in FY 1999 and FY 2000 have enabled NIH to initiate many new and important basic and clinical research programs, some of which are highlighted in the following pages. An increased investment in medical research continues to provide enormous benefits in the form of new knowledge, new treatments, new diagnostics, new preventions, and new interventions to decrease mortality and morbidity, and improve the quality of life for those who suffer from disease and disability. The rate of our progress is directly related to the creativity of our researchers and is only limited by the resources made available to support medical research and the infrastructure that sustains it.

The following charts explain how the FY 2000 funding increase will be spent by research mechanism, accompanied by examples of new and expanded research supported with the FY 2000 increase.

RESEARCH PROJECT GRANTS (RPGs)

Share of the FY 2000 Increase (\$ in Millions)



Definition - Research project grants (RPGs) are the most common funding mechanism at NIH. These are generally initiated by the investigator and used to support scientific research or training. A research grant provides a commitment of support for an average of four years of funding. Thus, after the competing year, the grantee receives noncompeting continuations each year for the specified length of the grant. The bulk of funding allocated to RPGs supports noncompeting continuations that allow important research to continue.

RPG Budget Distribution - FY 2000

61% of the increase
 58% of total budget
 8,950 competing grants
 32,942 total grants (w/SBIR/STTR)
 \$10,293m = total Research Projects

RPG Budget Increase Breakout

- < \$ 802m - To support continuing research
- < \$ 127m - To support 385 additional competing grants or new research
- < \$ 310m - To increase the average cost of all 8,950 competing grants by 12.3% and provide for program expansion
- < \$ 47m - To pay legally required increase in Small Business Innovation Research/Small Technology Transfer Research
- < \$ 5m - To further support Biomedical Information Science and Technology Initiative through the National Library of Medicine
- < \$ 33m - To further support Cancer Control
- < \$1,324m - of the \$2,180m increase

Selected FY 2000 RPG Programs

Characterize Molecular Profiles of Precancerous and Cancerous Cells. Understanding the sequence of changes a cell undergoes as it transforms from normal to cancerous can be used to identify new targets, at the molecular level, for effective prevention and treatment. This initiative seeks to complete an index of the genes expressed in cells at all stages of tumor development; establish molecular profiles of human cancer and develop molecular classification schemes for all human cancers; and develop databases and analytic tools for comprehensive molecular analysis. This research will lead to new and varied treatments for different forms of cancer.

Discovery, Development, and Testing of New Cancer Drugs. Consortia that develop and utilize cutting-edge drug discovery technologies will complement programs that foster the rapid development of promising molecules into drugs. New and ongoing efforts to improve the effectiveness and efficiency of, and access to, cancer clinical trials facilitate the critical transition from laboratory to clinical practice.

Preclinical Mouse Models. Models that truly reflect the behavior of human cancer and its response to preventive and therapeutic maneuvers would profoundly improve our ability to understand the process of malignant transformation, which would lead to much more effective cancer therapies. This initiative seeks to accelerate the Mouse Cancer Genome Anatomy Project to define the molecular anatomy of mouse cancer models; expand the number of mouse models for human cancer; test early detection, diagnostic, imaging, and prevention and therapeutic interventions in mouse models; and develop new tissue, cellular, and computational models of cancer.

Oxygen Sensing During Intermittent Hypoxia. Clarification of the molecular events occurring during intermittent hypoxia (deficiency in the amount of oxygen reaching bodily tissues) opens up possibilities for new ways to study hypoxia-related pathology in a wide range of tissues. This initiative seeks to improve understanding of how intermittent hypoxia contributes to the course of cardiopulmonary and cerebrovascular disorders.

Electrical Remodeling: Novel Opportunities for Arrhythmia Control. Electrical remodeling is a persistent change in cardiac characteristics that occurs after a temporary, abnormal heart rhythm change. This initiative is directed at elucidating the processes that influence cardiac remodeling at the molecular, cellular, tissue, and organ levels. Electrical remodeling provides new opportunities for development of novel arrhythmia control and prevention strategies before persistent changes in cardiac electrical characteristics occur.

Positional Candidate Gene Approaches in Asthma Gene Discovery. The goal of this initiative is to identify the gene or genes in a particular region that are linked to asthma or asthma-associated phenotypes. Identification of asthma susceptibility genes will aid in deciphering the molecular mechanisms predisposing to asthma and should lead to development of safer and more effective therapies. The near completion of the human genome project and the development of technologies to analyze genetic material should greatly facilitate the search for genes linked to various chromosomal regions.

Restoring Function Following Spinal Cord Injury. Restoring function following spinal cord injury remains a high priority because of the burden of spinal cord injuries and the potential for applying advances in basic neuroscience toward this problem. Initiatives in spinal cord injury will be expanded in several new areas, such as the spinal cord mapping anatomy project to determine the temporal and spatial changes in gene expression following injury, and understanding spinal cord circuits in the normal and injured spinal cord in order to explore modulating those circuits by electrical or chemical intervention.

National Programs of Excellence in Neuroinformatics. By facilitating collaboration between informatics scientists and neuroscientists, this initiative will provide the means to develop advanced computerized management systems of data on the nervous system. These data systems must make the data accessible, interactive, and interpretable to researchers and clinicians working in different environments and at distant locations. This initiative may lead to new insights into brain structure and function, and ultimately to advancing understanding of the brain in health and disease.

Civilian Defense from Bioterrorist Attack. This program seeks to design and develop safe and effective treatments and vaccines to be used in the event of a bioterrorist attack. Since many disease-causing organisms which might be used as bioterrorist weapons are rare or emerging, defense measures developed for bioterrorism should have broad applicability for global health even in the absence of a bioterrorist attack.

HIV Therapeutics: Targeting Research Gaps. Despite the apparent maturity of the HIV therapeutics field, many research gaps persist. This initiative aims to optimize and complement existing treatment modalities through research to enhance drug delivery, discover viral proteins that can be targets of future therapeutics, develop new paradigms for targeting and eliminating HIV cellular reservoirs, find vectors for direct, *in vivo*, delivery of therapeutic genes and vaccines, and learn how to manipulate innate immune components.

Hepatitis C Virus (HCV) Cooperative Research Units and Centers. Renewal and expansion of this multidisciplinary basic research program will enable the centers to broaden the research areas covered, e.g., to explore the implications of different transmission routes, and to better address the impact of this disease on minority populations. The new HCV research units are new vehicles that complement the centers in the effort to understand HCV pathogenesis and natural history. The research units and centers are part of a larger strategy to address HCV that includes work on model systems and vaccine and therapy research. This multifaceted but coordinated strategy emerged from planning efforts that included an NIH Consensus Development Conference.

Vaccine Immunology Basic Research Centers. These centers will bring together basic immunologists, clinicians, and infectious disease experts to address key problems in vaccine development for specific infectious diseases. The development of effective prophylactic and therapeutic vaccines for serious diseases such as tuberculosis, malaria, and hepatitis C, requires new approaches to vaccination. Areas under study include channeling appropriate cellular and humoral responses, circumventing immune evasion by pathogens, uncovering new molecular targets for vaccines, and developing potent adjuvants. Recent advances in basic immunology provide a promising foundation for vigorous multidisciplinary collaboration at the Vaccine Immunology Basic Research Centers in order to develop such capabilities.

Protein Structure Initiative. This initiative will follow the ongoing successful sequencing of the human genome and has as its goal the determination of the structure and function of all proteins. Recent technological advances and anticipated future technological developments in protein structural determinations makes this formidable task feasible.

Cryoelectron Microscopy. This initiative will further develop the capabilities of electron microscopy for rapid determination of the structure of complex protein structures in the cell. The recent successful elucidation of the structure of the ribosome demonstrates the value of this research tool.

Health Disparities in Drug Abuse. This initiative will support the continued efforts in all areas of research, including basic, clinical, and epidemiological, to increase understanding of the link between drug abuse and various diseases that predominantly affect underserved populations. This knowledge will be needed to develop treatments, interventions, and prevention programs that are gender, age, and culturally relevant to these populations.

Early Origins of Structural/Functional Impairments and Adult Disease. This initiative will involve a series of coordinated projects that target the intrauterine period and early childhood for identifying both the genetic and non-genetic traits that determine susceptibility to disease. The findings from this research will be used to develop diagnostic products to predict disease susceptibility, design novel therapeutics, and optimize current therapies.

Global Network for Women and Children's Health Research. This initiative will begin to explore the basic, behavioral, and translational research questions that are essential for informing public health and medical practitioners and improving the health of women and children. Areas of study include global infectious diseases; leading causes of infant and child mortality and morbidity; and women's reproductive health, especially in under developed countries.

Environmental Etiology of Parkinson's Disease. Parkinson's Disease usually strikes during the most productive time in adult life (mid-40s), leading to a loss of motor coordination, posture instability, tremors, dementia, and ultimately, death. Three initiatives will be launched in order to gain an understanding of the environmental etiology of this disease: advances in molecular and structural biology; epidemiology studies; and career development of physician/scientists.

Alzheimer's Disease Prevention Initiative. The goal of this research is to develop interventions that prevent Alzheimer's disease (AD) from manifesting clinically, as well as slow the progression of the disease once it is diagnosed. The Initiative will accelerate discovery of new risk and protective factors, identify promising targets for preventing disease, speed drug discovery and movement of promising new treatments and prevention strategies into clinical trials, launch clinical trials to prevent AD, and expand strategies for improving patient care and alleviating caregiver burdens.

Trans-NIH Initiative on the Demography of Health. This initiative will focus on the impact of global population aging, especially with respect to the burden of chronic disease and disability and related health and economic trends. This will include new approaches to generalizing findings from clinical trials to the broad population, as well as comparison of the economic incentives in medical care systems and the effect of these on the allocation of resources and other outcomes across population groups.

National Elder Abuse and Neglect Initiative. The time is right for a carefully designed national study of elder abuse and neglect--data on the problem is lacking, there are growing numbers of older people, increasing public awareness of the problem, and legal requirements for reporting the problems. In addition, there are recent methodological advances and research-based interventions to facilitate prevention and treatment programs. This initiative will focus on issues related to the detection of stigmatized and illicit behavior plus alternative designs to calibrate methods. It will also support an expanded national probability survey of elder abuse and neglect, and intervention research on the prevalence of abuse/neglect.

Providing the Science Base for Caregiving Policies and Programs. Demographic changes in families and increasing labor force participation of women suggest challenges ahead for the provision of informal care for aging baby boomers. This project will support the development of data that is needed to examine caregiving needs, patterns of family caregiving, how people make decisions on providing care, and costs of care.

Early Identification and Intervention for Young Children and Infants with Hearing Impairment and Other Communication Disorders. There have been few well-controlled studies to assess the relative efficacy of intervention strategies in infants and children with hearing impairment or other communication disorders. This initiative will support the development and validation of intervention strategies that are tailored to the individual, taking into account the family environment, socioeconomic variables, severity of disorder, age of diagnosis, and the specific type of intervention.

Diagnostic Tests to Identify Mutations in Genes that Result in Hearing Impairment. With the identification of genes that contribute to hearing function, genetic testing becomes possible. This initiative will address important unresolved issues, such as the prevalence and effect of mutations in various populations, the clinical significance of these mutations, and the short and long-term impact of such testing on individuals and their families.

Human Genetic Studies of Vulnerability to Drug Addiction. Understanding the role of genes in vulnerability to addiction is critical to understanding the nature of addiction and will lead to far more effective prevention and treatment programming. This initiative will be expanded to stimulate development of new classification methods and to refine the definition and diagnosis of addiction; to develop statistical and mapping methodologies to better locate and identify genes that play a role in drug addiction.

Exploiting Neuroimaging Capacity. Advances in neuroimaging technologies have provided major opportunities to study the neurobiology of drug abuse and addiction in human subjects, and have been extremely useful in clarifying their underlying circuitry and mechanisms. This expanded initiative will lead to an increased understanding of abuse and addiction and ultimately to the development of more effective medications.

Identification of Genes Predisposing to Alcoholism . Approximately 60 percent of total-population vulnerability to alcoholism is mediated by genetic factors. Analysis of a new data set of chromosomal regions likely to contain genes that influence alcohol-related behavior will facilitate the identification of the genes that predispose to alcoholism, the development of new analytic methods; and identification of genetic bases for other disorders, such as smoking, that share a comorbidity with alcoholism.

Adolescent Alcohol Abuse Neurobiology. Research will be stimulated to use animal and human subjects to examine the neurobiological mechanisms and risk factors for alcoholism during late childhood through adolescence as well as the ascertainment of the relative contribution and/or interaction of neurobiological, genetic, environmental, and social factors (e.g., family history, stress, peer influences) in the development of adolescent alcohol abuse.

Targets of New Medications for Alcohol Induced Liver Damage and Cirrhosis. Cirrhosis of the liver is irreversible, and 40-90 percent of the US deaths from this disease are due to alcohol. Researchers recently found that alcohol-fed mice engineered to lack the action of a particular immune-system protein, tumor necrosis factor-alpha, do not develop this liver disease. Drugs developed recently for inflammatory diseases which inhibit tumor necrosis factor-alpha may be useful in combating liver cirrhosis, and further research is needed in this area.

Research on End of Life/Palliative Care. Recent achievements in medical research have extended the life of many Americans. This research will continue to focus on symptom management, communication, and decision-making issues associated with dying.

Self-Management Strategies Across Chronic Disease. With an aging population, chronic diseases will increase proportionately. Children and young people who have a chronic disease can expect to live longer, and therefore, will need to manage their health condition(s) over a longer life span than in the past. This initiative will support research to test the effectiveness of interventions for self-management across chronic diseases and across specific subgroups of chronic diseases.

Empirical and Theoretical Foundation for Using SNPs. Discovery of human single nucleotide polymorphisms (SNPs)--single base-pair misspellings in DNA that may be associated with disease susceptibility or response to drugs--is now proceeding at a rapid rate. Yet efficient computational and experimental methods needed to use these SNPs effectively are not yet at hand. This program will support the development of these methods.

Technologies for Small Animal Imaging Research. The mouse has emerged as a critical model for understanding the role of environmental and genetic factors in disease. Improved imaging systems are needed for more complex and detailed studies involving mouse models. This initiative will support the exploration of new technologies and novel encoding methods that can be applied to the imaging of small animals and for refining and improving existing technologies.

Quick-Trials for Novel Cancer Therapies. This initiative will support pilot, phase I, and phase II clinical trials and associated patient monitoring and laboratory studies for the treatment of malignancies using new therapeutic approaches. Quick-Trials will involve a simplified grant application process and rapid turnaround from application to funding.

Traditional and Indigenous Systems of Medicine. Approximately two-thirds of the world's population seek alternative and complementary medicine practices. This initiative will pave the way for full-scale, randomized, clinical trials exploring the use of traditional, indigenous systems of medicine as practiced in the United States.

Plasticity in Developing and Adult Brains. Recent research has revealed an exciting finding that new brain cells can be generated in certain parts of the adult brain. New research projects will focus on the genetic, biochemical, and physiological basis for this plasticity (ability to regenerate), as well as its role in learning and in the formation of connections, or synapses, between brain cells.

Clinical Trials: Methodology Improvement and Ancillary Studies in Mental Health. Research programs will be sponsored to improve the design and analysis of clinical trials of therapies for depression, anxiety disorders, schizophrenia, and other mental disorders. This research will include natural history studies; population-based studies in pharmacokinetics and pharmacogenetics; application of biomarkers and imaging studies; development of new symptom scales and screening and diagnostic tools; biostatistical approaches to data analysis; and development of clinical measuring instruments.

Control of Angiogenesis. The development of new blood vessels (angiogenesis) is an important process involved in development and in many diseases. Research projects will focus on the role of angiogenesis in various eye diseases that occur in association with aging, diabetes, and prematurity. Special emphasis will be placed on understanding the effects of various growth factors and proliferative agents on blood vessels. Research projects will range from animal model studies to clinical research.

Novel Instruments for Microimaging. Funding will support the development of a range of technologies for visualizing three-dimensional biological structures and molecular and cellular processes. This will include high speed multi-photon microscopy and development of software for analyzing a variety of complex microimaging datasets.

International Cooperative Biodiversity Group Awards. This interagency program supports interdisciplinary research to discover new drugs from plants, animals, and organisms in combination with analysis of the distribution and ecology of these organisms and potential measures to deter loss of habitats.

Ecology of Infectious Diseases Program. This new interagency program will support interdisciplinary research projects on the ecology of infectious diseases that may be related to rapid environmental changes such as biodiversity loss, habitat transformation, environmental contamination, and other large-scale ecological events.

Combination Therapies for the Treatment of Osteoporosis. Research efforts will be expanded in this area to encompass funding of an additional multi-center clinical trial which will test the efficacy of combining parathyroid hormone and alendronate in the treatment of osteoporosis.

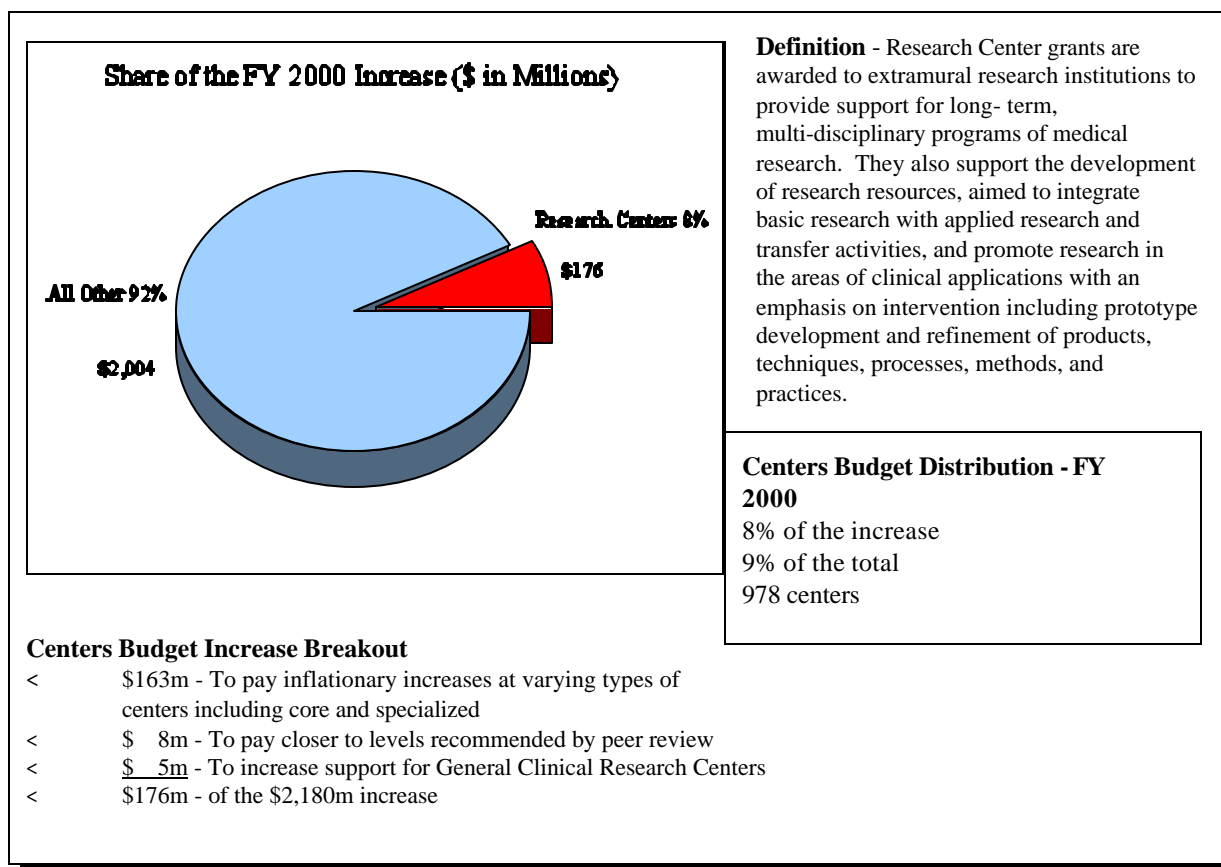
Mechanisms of Chondroprotection. Enhanced efforts will be undertaken that are targeted toward identification and evaluation of agents to prevent cartilage destruction and/or facilitate its repair in such conditions as rheumatoid arthritis, juvenile rheumatoid arthritis, and osteoarthritis.

Prevention of Diabetes and Its Complications in Minority Populations. Research programs will be expanded to evaluate racial and ethnic differences in the etiology of type 2 diabetes. Investigations will focus on differences in fat metabolism, energy expenditure, insulin resistance, glucose tolerance, and beta cell function. In addition, behavioral studies will explore socioeconomic, psychosocial, cultural and family and community factors that influence the development of diabetes.

Health Effects of Obesity. Research programs will be expanded to understand the health outcomes associated with obesity. An expansion of the Study of Health Outcomes of Weight-loss (SHOW) clinical trial will enable researchers to evaluate complications of obesity such as atherosclerosis, musculoskeletal abnormalities, glucose intolerance, and other comorbid conditions. Ancillary studies will be done in conjunction with the SHOW trial to evaluate multidisciplinary approaches to weight loss intervention programs.

Type 2 Diabetes in Children. An alarming increase in type 2 diabetes has been observed in children and the data indicate that obesity is a major risk factor for the rising incidence. This initiative will stimulate epidemiologic, metabolic, and clinical research to better characterize this form of type 2 diabetes in children. These studies will define early markers of insulin resistance and beta cell dysfunction, evaluate cardiovascular complications, and define genetic and metabolic differences in the occurrence of type 2 diabetes in various ethnic and racial populations.

CENTERS



Selected FY 2000 Centers

Tropical Medicine Research Centers. Applications are being accepted for multiproject center grants from institutions in geographic areas where tropical infectious diseases are endemic. The objective is to develop a flexible tropical disease research network that can be responsive to emerging scientific needs and challenges in the field of tropical infectious diseases.

Learning Disabilities: Multi-Disciplinary Research Centers. The objective is to identify the behavioral and neurobiological mechanisms that are influential in the expression of learning disabilities. Projects will focus on the development of preventive and treatment approaches to ameliorate learning disorders.

Comprehensive Centers on Health Disparities. These Centers will focus on cancer screening and management, as well as cardiovascular disease and stroke. The initiative will capitalize on the expanded research capacity that has been developed at medical schools affiliated with Research Centers in Minority Institutions and the collaborative research partnerships with more research-intensive universities.

Centers for Dietary Supplements Research. This initiative will foster interdisciplinary research to investigate the biological effects of botanicals, including, but not limited to, botanicals available as dietary supplements. A major goal is to identify potential health benefits of botanicals and to address concerns about the safety of botanicals, particularly those available as dietary supplements.

Human Genomic Sequencing Centers. A “working draft” sequence of the human genome representing at least 90 percent of the complete sequence will be finished in late FY 2000. In order to achieve this momentous milestone, additional investment is being made in centers conducting human sequencing.

Mouse Genomic Sequencing Centers. Expanded support for mouse genomic sequencing centers will ensure rapid progress toward goals of achieving a draft mouse genomic sequence by early 2002, 10-fold sequence coverage by 2003, and the complete, high-quality sequence within another 1-2 years.

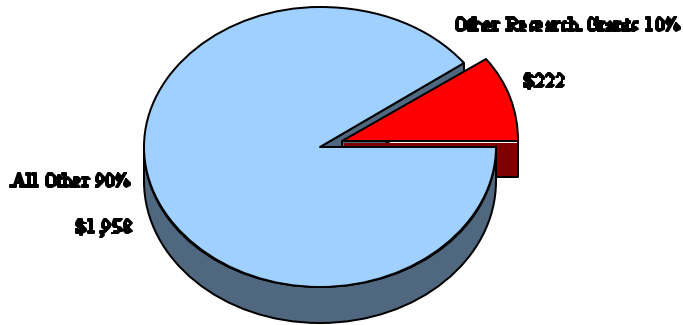
Improving Synchrotron Access through Beamline Construction and Upgrades. Compared to laboratory-based x-ray sources, synchrotrons provide increased rates of data acquisition, higher overall data quality, and the capacity to work with microcrystals. This initiative will support the development of new synchrotron beamlines for structural biology research and will begin to address a projected shortfall in beamline availability.

Distributed Phenotyping Resources for Animal Model Studies. This initiative will support the development, coordination, and expansion of technologies and resources for analyzing gene expression in genetically modified and normal animals, including mice, rats, fish, and other species used in medical research.

Centers for Complementary and Alternative Medicine Research. Despite the broad use of complementary and alternative medicines (CAM) there is a relative paucity of data available to demonstrate convincingly the safety, efficacy, effectiveness and mechanisms of these CAM practices. To promote high-quality CAM research, the NIH invites applications for Asthma and Cancer Centers for CAM Research which will provide the resources necessary for the rigorous scientific investigation of CAM.

OTHER RESEARCH PROGRAMS

Share of the FY 2000 Increase (\$ in Millions)



Definition - Other Research comprises a number of activities, including:

Research Career Programs (K awards) -

Designed to provide increased career opportunities in medical research to scientists of superior potential. The program provides support for young investigators who desire advanced development and scientists who need experience to qualify for senior positions. Included within this category are the following awards: Research Career Development Awards, Clinical Investigator Awards, Academic Investigator Awards, Career Transition Awards, Special Emphasis Research Career Awards, and Physician/Scientist Development Awards.

Cancer Education Program - Grants awarded to schools of medicine, dentistry, public

health, and nursing (with Ph.D. programs) and to teaching hospitals affiliated with medical schools. The grantee institutions develop and adopt curricula in cancer prevention, epidemiology, and nutrition. Students participate for 6-10 weeks per year in ongoing cancer research.

Cooperative Clinical Research - Grants awarded to multiple institutions where investigators are asked to follow common research protocols, because there are insufficient numbers of subjects available at a single institution to conduct a major clinical trial. NIH staff is substantially involved in the management of these awards.

Biomedical Research Support (BRS) - Grants awarded to NIH-supported institutions to fund shared instrumentation needs.

Minority Biomedical Research Support (MBRS) - Designed to increase the number and quality of ethnic minority biomedical research scientists by strengthening the capability of eligible institutions to conduct quality research in the health sciences and to support undergraduate students in biomedical research at minority institutions.

Other Research Related Grants - Various small grants, including scientific review and evaluation, small instrumentation, and conference grants.

Other Research Budget Increase Breakout

- < \$ 61m - To support ongoing outyears of grants
- < \$ 59m - To pay closer to levels recommended by peer review
- < \$ 68m - To revitalize clinical research by initiating K23, K24, K30 awards
- < \$ 10m - To increase support to Biomedical Research Support Grants
- < \$ 24m - To increase support to Minority Biomedical Research Support Grants
- < \$222m - of the \$2,180m increase

Other Research Budget

Distribution - FY 2000

10% of the increase
6% of the total
4,891 other research grants
\$1,031m = total Other Research

Selected FY 2000 Other Research Programs

Mentored Quantitative Research Career Development Award (K25). The goal of this program is to foster interdisciplinary collaboration in biomedical and behavioral research by supporting supervised research experiences for scientists with quantitative and engineering backgrounds. This award provides research and career development opportunities for scientists and engineers with little or no biomedical or behavioral research experience who are committed to establishing themselves in careers as independent biomedical or behavioral investigators. Examples of quantitative scientific and technical backgrounds outside of biology and medicine considered appropriate for this award include, but are not limited to mathematics, statistics, computer science, informatics, physics, chemistry, and engineering.

Institutional Awards for Didactic Training for Clinical Researchers (K30). This award, will continue to develop new didactic programs in clinical research at health sciences training institutions that do not currently offer such programs, or in institutions with existing didactic programs in clinical research, to support or expand their programs or to improve the quality of instruction. The goal of this program is to improve the training of clinical researchers, so that upon completion of their training, they can more effectively compete for research funding.

Mentored Training in Clinical Research Methodology Award (K23). Increased and sustained funding for young researchers is needed to attract talented people to clinical research and encourage them to remain in this career path. The K23 award supports the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a period of supervised study and research for clinically-trained health professionals who have the potential to become productive clinical investigators focusing on patient-oriented research.

Midcareer Investigator Award in Patient-Oriented Research Award (K24). This award program provides support to midcareer clinical investigators for training new clinical researchers. The program provides the means for the mentors to take time from patient care and administrative responsibilities and devote it to patient-oriented research and mentoring of new clinical investigators.

Senior Scientist Award (K05). The K05 award permits stable support to outstanding scientists who have demonstrated a sustained, high level of productivity and whose expertise, research accomplishments, and contributions to the field have been and will continue to be critical to the mission of the NIH. The award provides salary support for award periods of up to five years as a means of enhancing the individual recipient's skills and dedication to his/her area of research.

Mentored Research Scientist Award (K01). This program provides support for an intensive, supervised career development experience in biomedical, behavioral, or clinical sciences leading to research independence. By expanding the research skills and knowledge of investigators, the KO1 program sustains the professional research workforce in a broad range of areas of investigation and enhances faculty development from represented groups or faculty development at minority-serving institutions.

Expand National Research Infrastructure on Tobacco Use/Prevention. We have an unprecedented opportunity to reduce the enormous burden of tobacco use on our Nation's public health. This initiative will expand the national research infrastructure on tobacco use and prevention by supporting additional Transdisciplinary Tobacco Use Research Centers and funding transdisciplinary research and training programs, especially for minority physician scientists and post-doctoral fellows.

Gene Variants in Key Molecular Pathways. Identifying cancer-related genes and their variants is critical to increasing our understanding of what causes cancers, how they develop, and how best to prevent or treat cancers. We can now examine a wider variety of cancers and extend our discovery process to include not only cells that play key supporting roles in cancer development, but also body fluids that might contain early indications of cancer development.

Expand and Improve Clinical Studies of Imaging Modalities and Image-Guided Interventions. Advances in technology and science are fueling the development and improvement of all kinds of diagnostic imaging tools. This initiative will expedite the integration of diagnostic imaging technologies into clinical trials; develop non-invasive imaging technologies for the localization, biopsy, and minimally invasive treatment of prostate cancer; and develop and evaluate imaging technologies.

Diabetes Genome Anatomy Program. Diabetes mellitus is a multigene disorder that affects virtually every tissue of the body, resulting in long-term and severe damage. The focus of this initiative is to obtain genomic information on the spectrum of genes active in diabetes and its complications to aid in disease prevention and in the development of new and better diagnostics and therapies.

Biotechnology Consortia for Gene Profiling Program. The Human Genome Project and related efforts to identify at least some unique pieces of all the active genes in the human genome have resulted in an explosion of data and potential tools, which will aid in research in virtually all fields of medicine. The purpose of this initiative is to make comprehensive gene activity technologies widely available to researchers working in the areas of diabetes and digestive and kidney diseases.

Infrastructure, Shared Resources, and Consortia. This expanded program will provide the infrastructure for neuroscience in the coming years. Shared neuroscience facilities are particularly needed for molecular genetics, neuroimaging, informatics, the development and use of animal models, and electrophysiological, anatomical, and cellular studies.

Glue Grants. Many central programs in biology can no longer be addressed using the resources, intellectual and material, found in a single investigator's laboratory. The primary goal of this initiative is to provide the "glue" for existing R01 investigators to collaborate in attacking major research questions that require a significant investment and a broad range of tools and skills.

Enhancement of Support for the Minority Biomedical Research Program. The NIH and the Indian Health Service are collaborating to improve and expand health research involving American Indian and Alaska Native tribes and people. The goal is to enhance and expand the capacity and skills of tribal organizations and Native American researchers to conduct high quality biomedical and behavioral health research and to apply successfully for competitive government and non-government research grants.

Understanding the Disability Decline and its Demographic and Economic Implications. Consistent evidence of a decline in disability rates has been found and is important not only because functional ability is a key aspect of individual well-being, but also because it may moderate other important aspects of population aging. This initiative will identify and analyze the underlying causes of the decline in disability.

Software, Hardware, & Strategies for Neuroinformatics. The quantity and complexity of data derived from brain imaging and other areas of basic and clinical neuroscience research necessitate a global neuroscience information management system. This initiative will focus on software and hardware tools

for brain imaging data; a central resource to facilitate and allow the sharing of collaborative software with the research community; a central repository for data deposition, storage, and shared analysis by the research community; and partnership with US, the European Union and other countries.

Research on Mental Health and Violence in Children and Adolescents. Violent behavior—especially by youth—is commanding increasing attention as a major public health problem, raising national concern for finding effective approaches to preventing and reducing violence. This program encourages new studies to clarify relationships between mental disorders and youth violence and suicide, including research to prevent the emergence of syndromes and disorders, and to interrupt the development, escalation, and/or continuation of serious conduct problems, violent behavior, and other co-occurring disorders.

Early Intervention & Treatment for Children & Adolescents with Mental Disorders. Early detection and treatment of mental disorders may result in a better prognostic and functional outcome in adult life. This initiative includes research on modifiable risk factors for eating disorders; new interventions to prevent exacerbation of, and functional impairments associated with, depression and anxiety in children; the long-term impact of early intervention; and long-term effectiveness and safety of treatment interventions for patients with chronic or recurrent disorders.

Clinical Trials Network (CTN). The CTN is serving not only as an infrastructure for testing science-based treatments in diverse patient populations and treatment settings, but also as a mechanism for promoting the rapid translation of new treatment components into actual community clinical settings throughout the nation. The network will be expanded so that more patients in need of drug addiction treatment can participate in these trials. By teaming researchers with community treatment practitioners to test science-based treatments in real life settings, a dramatic leap forward is being made toward improving national drug abuse treatment.

Infrastructure Focusing on Reducing Health Disparities - Career Development. In an ongoing commitment to understand and reduce health disparities, NIH will expand efforts in the Career Development program, with a special emphasis on health disparity and minority health projects.

Advanced Development of Genomics Technology. A number of promising new technologies that will make DNA sequencing cheaper and faster are at the point where they need to be tested in a production environment. This program will provide funding to enable these technologies to be tested and brought to a robust state where they can be used in high-throughput mode.

Shared Instrumentation. The Shared Instrumentation Grant Program will be expanded to meet the increasing needs of the community for instruments in the \$100,000-\$500,000 cost range. In the post-sequencing era, more and more basic and clinical investigators, many of whom were not dependent on instruments previously, have become reliant on new high-throughput, highly sensitive, expensive research tools.

New and Expanded Clinical Research Career Development Opportunities. A new program to support a medical student mentored clinical research training program is intended to serve as a catalyst for young physicians to pursue careers in patient-oriented research. In addition, the Clinical Research Scholars program will be reinstated.

International Consultations and Training in Bioethics. International training will be expanded to increase the cadre of professional investigators and other health professionals with state-of-the-art understanding of the ethical considerations, concepts, and methods in human subjects research. The purpose of this program is to assist current and future investigators to pursue culturally relevant studies on ethical theory and practice in biomedical and behavioral research and to enable these individuals to provide expertise to their host institutions, national governments, and international bodies.

Health and Economic Development. Research will focus on the causal links between health, macro-economic and house-hold level growth, and broader indicators of development. The initiative will examine the effect of health status and demographic characteristics on such indices as gross domestic product and per capita income, agricultural and manufacturing productivity, literacy and social and environmental welfare. Health interventions can then be evaluated by an expanded set of criteria useful for setting priorities.

Supporting Extramural Training. There is a significant shortage of professionals with training in both biomedical and computer science to conduct informatics research and to apply the research results in practice to health care delivery and research. To help remedy the manpower gap, NIH is expanding training programs at universities across the nation for the express purpose of training experts to carry out research in general informatics and in the genome-related specialty of bioinformatics.

International Malaria Research Training Program Award. This institutional award program will help develop and expand the capabilities of scientists and health professionals by developing innovative, collaborative malaria research training programs. The goal is to harness scientific knowledge and skills to improve prevention strategies for malaria and related morbidity and mortality, and to control malaria transmission in endemic developing countries.

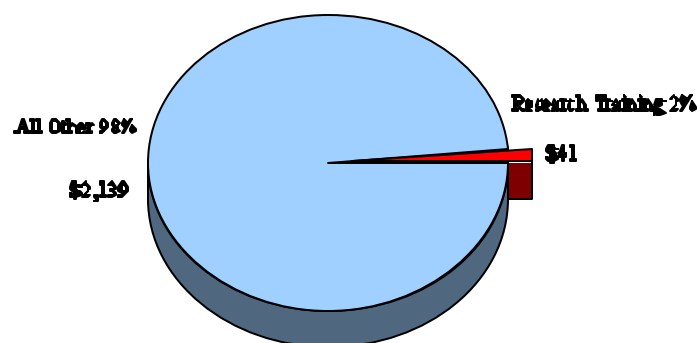
AIDS International Training and Research Program. This program will support training in biomedical and behavioral HIV/AIDS-related prevention and related tuberculosis research as well as data management analysis in support of this research. This program will help facilitate new prevention research efforts and establish cooperative relationships between U.S. and foreign researcher groups.

Minority International Research Training Grants. This training program supports career development for groups underrepresented in biomedical and behavioral research. The program is designed to provide training for undergraduate, graduate, and medical students in international research settings. This training program is a component of NIH research strategies to reduce health disparities among minority and majority groups in the U.S.

International Training and Research Program in Population Health. The objectives of this program are to support training in, and international collaborative studies of, reproductive processes, reproductive epidemiology, contraceptive development, and social and behavioral factors that influence population dynamics. This initiative will help scientists from developing nations contribute to global population research efforts, advance knowledge in support of population policies for their countries, and establish international guidelines.

RESEARCH TRAINING

Share of the FY 2000 Increase (\$ in Millions)



Definition -The National Research Service Awards (NRSA) program serves to replenish the Nation's corps of biomedical and behavioral research investigators. Through institutional awards and individual fellowships, NIH supports both basic and applied research training in the biomedical and behavioral sciences. Institutional awards provide the foundation for the manpower development effort by supporting the national capacity for excellent, up-to-date training in a variety of institutional settings. They enable NIH to aid institutions in maintaining vigorous and effective research training programs and, in particular, to support research training programs in areas of national need. Decisions on the number of research trainees to be supported by NIH are based upon assessment of program needs and opportunities by the NIH Institutes, the NIH Director, recommendations of the National

Academy of Sciences (NAS) and other

groups, and the

availability of funds.

Research Training Budget Increase Breakout

- < \$37m - To increase stipends, health insurance, and institutional allowances
- < \$ 4m - To support an additional 135 fellows and trainees
- < \$41m - of the \$2,180m increase

Research Training Budget

Distribution - FY 2000

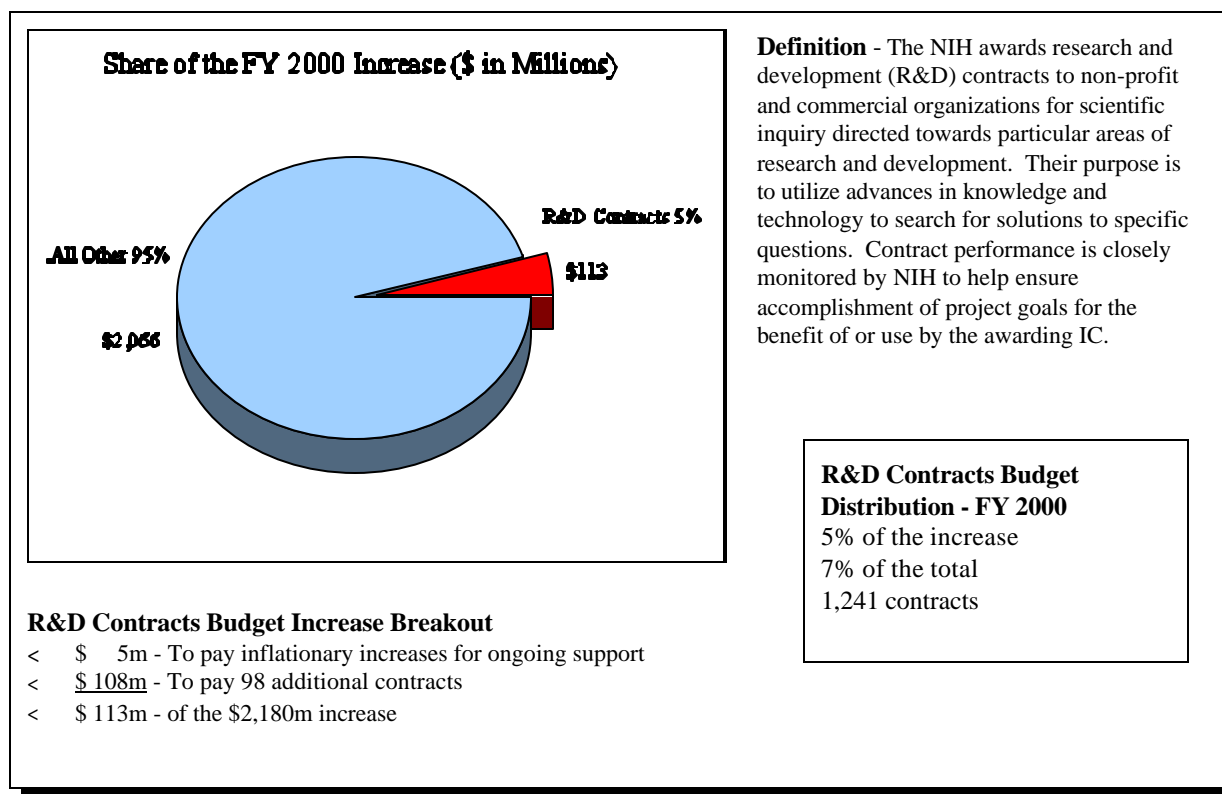
- 2% of the increase
- 3% of the total
- 15,874 NRSA's
- \$550m = total Research Training

Selected FY 2000 Programs in Research Training

Postdoctoral Fellowships in Genomics and Related Ethical, Legal and Social Implications. This fellowship program supports the growing need for scientists and scholars who are trained in a variety of disciplines to accomplish the goals of the Human Genome Project and use the knowledge, research, and data to address future research questions. Broad areas of research related to genomics will be included such as technology development, and the ethical, legal, and social implications of human genetic research.

Predoctoral Research Training in Complementary and Alternative Medicine. NIH will provide predoctoral research training in specific areas of biomedical and behavioral research to ensure that highly trained scientists will be available in adequate numbers and in appropriate research areas and fields to meet the nation's health research needs in complementary and alternative practices of medicine.

RESEARCH AND DEVELOPMENT CONTRACTS



Selected FY 2000 Contracts

Making Molecules into Drugs. This initiative includes new and ongoing efforts to improve the effectiveness and efficiency of, and access to, cancer clinical trials to facilitate the critical transition from laboratory to clinical practice. Consortia that develop and utilize cutting-edge drug discovery technologies will complement programs that foster the rapid development of promising molecules into drugs.

New Crystallographic Synchrotron Beamline Station at Argonne National Labs. The value of synchrotron radiation as an essential tool for determining highly complex protein structures is increasingly clear. Because there are a limited number of beamlines, however, researchers face long delays in obtaining access to synchrotron facilities. NIH is planning the construction of two new state-of-the-art beamline stations at the Advanced Photon source at Argonne National Labs.

Employing Informatics to Accelerate Cancer Research. Advances in computing and telecommunications are enabling scientists to collaborate and generate incredible amounts of biological information. So that this information can be fully utilized and shared, NIH is developing a knowledge management system – the Cancer Informatics Infrastructure – to help capture, analyze, and apply information from cancer research.

Whole Genome Approaches to Pathogen Research. Whole genome sequencing is a cost-effective and efficient means of gene discovery and of providing information needed to define gene function and

expression. This initiative will provide resources needed to explore the genomes of microbes that cause disease in humans. The availability of whole genome sequences for human pathogens has the potential to revolutionize research approaches to questions of pathogenesis and microbial biology, and development of new diagnostic, treatment and interventions strategies.

Collaborative Network for Clinical Research on Immune Tolerance-Asthma and Allergic Diseases.

Despite the availability of proven therapies for treating asthma and allergic diseases, even the most effective pharmacotherapies have serious limitations. This initiative will support additional studies in asthma and allergic diseases, including clinical trials of the safety, toxicity and efficacy of tolerance induction treatment regimens; integrated studies of the underlying mechanisms of the induction, maintenance, and loss of tolerance; and the development and validation of assays and immune markers of immune tolerance in humans. This research is the first step toward developing new therapies.

National Longitudinal Mortality Study. To gain an understanding of the powerful and changing influence of socioeconomic status, this program will collect and analyze information on social and economic factors in relation to death by cause. The study will be based on a national sample of 2 million persons, of whom 200,000 have died.

Promoting Repair & Plasticity with Neural Stem Cells. Stem cells are capable of reproducing themselves and of producing cells that can develop into the full range of specialized cells present in a particular organ or tissue. There are increasing applications of stem cells in both basic and clinical research. The goals of this initiative are to provide the infrastructure for posting detailed protocols for the generation and use of different types of neural stem cells, and to maintain well-characterized stem cell lines that will be readily available to investigators. This will optimize the use of neural stem cells, encourage translational research, and facilitate clinical applications using neural stem cells.

Eliminating Racial Disparities in Rates of Sudden Infant Death Syndrome (SIDS). The incidence of SIDS among African American babies is more than double that in the white population. Research on culturally-appropriate communication strategies for eliminating the racial disparity in infant sleeping position will be expanded and new Back-to-Sleep campaign materials appropriate to subgroups of caregivers of African American infants will be developed.

The Sister Study: Gene-Environment Interaction in Etiology of Breast Cancer. This new project is working to establish a study population of unaffected sisters of breast cancer patients to clarify the joint effects of environmental and genetic factors in the development of breast cancer. This population will allow researchers to examine breast cancer risk in relation to factors such as hormonally active environmental agents, hormones, growth factors, and environmental contaminants such as pesticides, and to study these factors jointly with genes involved in their activation and detoxification.

A National Twin Registry. This new initiative will develop a resource registry for enrollment of twins. Because identical twins share all their genes, whereas fraternal twins share about half of their genes, comparison of the similarity between the two types of twins allows one to estimate the relative importance of genes and environment. A national twin registry will increase the power of the Human Genome Project, both immediately and in perpetuity, at a fraction of the expense, and will be a valuable tool for analyzing complex diseases and diseases of uncertain heritability.

Environmental and Genetic Origins of Respiratory Diseases. To define the interactions between environmental and genetic parameters of asthma, studies are being conducted that capitalize on the fact that there is a marked geographical variation in rates of childhood asthma. Comparative studies of asthma risk factors among high- and low-incidence populations may help identify those factors that are related to disease development. Information to be generated by these studies will be critical to devising and choosing appropriate interventions and prevention strategies.

Genetics of the Brain & Mental Disorders. This expansion of the Brain Molecular Anatomy Project will permit comprehensive study of functional gene activity in mammalian systems. Related initiatives will focus on the functional genomics of mouse behavior and nervous system and on high resolution mapping of mental disorders and their biological underpinnings.

Medications for Stimulant Abuse and Overdose. There are relatively few medications currently available to treat addictions, and no medications currently approved for any aspect of stimulant abuse, addiction, or overdose. This initiative will significantly expand efforts to develop medications for stimulant abuse by examining the potential of a variety of new medications, testing the efficacy of certain compounds in clinical trials, and expanding studies of immunological approaches.

Technologies for Creating a “Biological Catalog” of the Genes of Humans, Mice, and Other Important Mammals. The availability of high quality full-length mammalian cDNAs is essential to research efforts to develop new and improved treatments, diagnostics, and prevention strategies. This initiative builds on and complements a number of high-priority NIH genome efforts, including the Human Genome Project, the Cancer Genome Anatomy Project, and the Brain Molecular Anatomy Project.

Informatics for the Heart Attack Alert Program. This groundbreaking program is evaluating the effectiveness of information technology in improving the timely use of heart attack therapies which are known to be highly effective in reducing death and disability. The program is evaluating a battery of technological approaches. If information technology can be shown to make a difference, we will have an important new technique for modifying behavior and improving health in the U.S.

Healthcare and the Next Generation Internet. Telemedicine and telehealth projects are documenting the value of advanced communications to health care, research, and public health as well as demonstrating why the current Internet must be replaced by a more powerful and robust Next Generation Internet (NGI). NIH is working to define NGI capabilities which will be needed if the NGI is to be used routinely in health care, public health and health education, and biomedical, and clinical and health services research.

Visible Human Project: From Data to Knowledge. The Visible Human Project is being expanded in three areas: development of a Visible Human Project Atlas of the Head and Neck, development of a tool kit of computational plug-ins for basic data handling functions, and new methods for stabilizing anatomical materials used in making the Visible Human datasets.

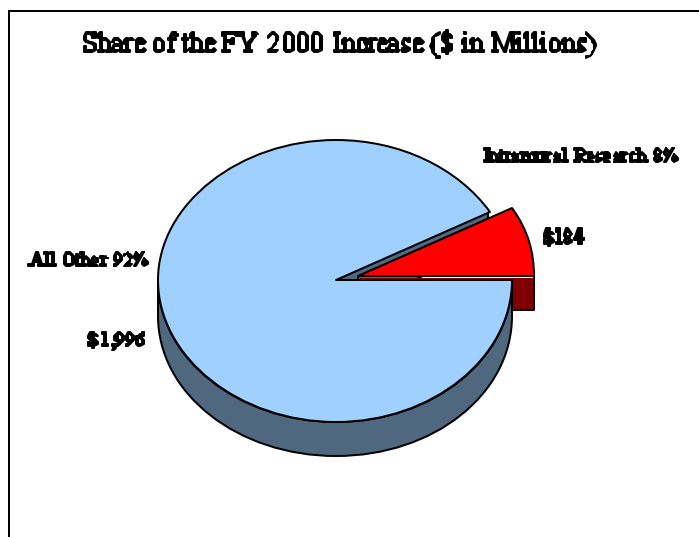
Collaborative Network for Clinical Research on Immune Tolerance-Asthma and Allergic Diseases. This initiative will expand the scope of research by the Collaborative Network for Clinical Research on Immune Tolerance. It will enable additional studies in asthma and allergic diseases, including clinical trials of the safety, toxicity, and efficacy of tolerance induction treatment regimens (by which a foreign substance, such as an allergen, becomes tolerated by an individual); integrated studies of the underlying

mechanisms of the induction, maintenance, and loss of tolerance; and the development and validation of assays and markers of immune tolerance in humans.

Studies in the Emergence of Antimicrobial Resistance in the 21st Century. New efforts will focus on antibacterial resistance in the hospital setting with an emphasis on clinical strategies to decrease the frequency of infection, reduce emergence of antimicrobial resistance, and rapidly detect infection and resistance. This initiative will target populations at increased risk for the development of infections.

Whole Genome Approaches to Pathogen Research. NIH is currently supporting more than 20 pathogen whole genome sequencing projects and the sequences of many other pathogens are already available in the public domain. This initiative will provide resources needed to optimally exploit the pathogen genome sequence information.

INTRAMURAL RESEARCH



Definition -Through the intramural research program, the NIH conducts basic and clinical research at its on-campus research facilities in Bethesda, Maryland, and at other campuses such as the Gerontology Research Center and the Addiction Research Program in Baltimore, Maryland; Research Triangle Park, North Carolina; the Rocky Mountain laboratories in Hamilton, Montana; and Phoenix, Arizona. The fundamental research performed by intramural scientists provides the basis upon which advances in medical care are built. An important byproduct of research productivity is the cadre of young physicians and basic scientists. One of the unique features of the NIH intramural research program is the close proximity of many of its research laboratories to the Clinical Center, a 300-350 bed research hospital on the NIH

campus. This provides an opportunity for bridging the gap between basic

basic and clinical science by carrying laboratory research to the bedside.

Intramural Research Budget Increase Breakout

- < \$ 24m - To pay salary adjustments
- < \$ 65m - For new research personnel and conversion of clinical fellows to Full-Time Equivalents
- < \$ 90m - Maintain existing laboratory programs, start-up for miscellaneous new programs
- < \$ 27m - Library operations
- < \$-32m - Buildings and Facilities
- < \$ 10m - Cancer Control Operations

Intramural Research Budget Distribution - FY 2000

8% of the increase
12% of the total
\$2,175m = total Intramural Research

Selected FY 2000 Intramural Programs

Surrogate Markers for Safety. Advances in identifying critical target genes in diseases coupled with new combinatorial chemistry and recombinant DNA approaches have led to the greatly accelerated discovery of new candidate drugs. Development of surrogate markers for clinical efficacy and safety is now a high priority. This expanded initiative will focus on the validation of surrogate markers for safety in order to permit the rapid detection of adverse drug effects in preclinical models and human clinical trials.

Innovative Technologies for Exposure Assessment: Linking Exposure to Human Disease. The application of advances in bioengineering imaging techniques and computational biology, coupled with the increasingly sensitive tools of analytic chemistry and gene expression/function, provide new opportunities to bridge the gap between exposure assessment and human disease. This expanded initiative will address several issues, including children's health; health disparities arising from disproportionate exposures;

development of biologically-based models for assessing low-dose risks arising from chemical exposures; and gene/environment interactions.

Genetic, Molecular and Cellular Basis of Age-Related Functional Senescence. This expanded initiative will foster a more comprehensive understanding of various aspects of age-related functional decline and senescence including: the genetic, molecular, and cellular basis of functional senescence; metabolic regulation and stress responses as determinants of aging and longevity; age-related changes in genomic instability; and age-related changes in the structure, composition, and function of the extracellular matrix.

PubMed Central. This Web-based repository of scientific research provides access to primary reports in the life sciences and is viewed as the initial site in an international system. PubMed central will archive, organize, and distribute peer-reviewed reports from journals, as well as reports that have been screened but not formally peer-reviewed. Expanded support will be provided for computer equipment and maintenance and for document conversion and personnel.

Health Information for the Public. The goal of this initiative is to provide a visible and usable NIH digital library of consumer health and patient education information that would be widely recognized as a source of current, authoritative information for the general public. Expanded support will be provided for twenty or more new projects involving partnerships between health science libraries, public libraries, health professional associations, public health departments, and/or community-based organizations and will provide training to public librarians in using the NIH information services.

Clinical Trials Database. The NIH Clinical Trials Database is a registry of clinical trials for both federally and privately supported trials of experimental treatments for serious or life-threatening diseases or conditions. The database includes summaries of the purpose of each clinical research study and its design, the phase of the trial, its recruiting status, the criteria for patient participation in the trial, the location of the trials, and specific contact information. Patients, families, and members of the public have easy access to information about clinical research studies that can help them decide whether to enroll in a particular trial.

Howard University Genetics Center. NIH and Howard University are collaborating in a series of studies on the genetic underpinnings of diseases that are particularly common in African Americans. The initial focus is on diabetes and prostate cancer.

Bone Clinic. This initiative seeks to establish a bench-to-bedside research program in skeletal diseases. It will build on existing strengths in skeletal biology basic science and will involve collaborations among various NIH Institutes.

Neurodegeneration in the Visual System. Expanded research programs will address how nerve cells of the retina are damaged and investigate the potential for regeneration of these cells. Projects will examine approaches to rescue photoreceptors through the use of growth factors, transplantation, and ribozymes and other forms of gene transfer. Additional research will study protection of the axons in the optic nerve in model systems for glaucoma, and evaluate certain biochemical trophic factors that appear to be involved in the survival and protection of retinal ganglion cells from cell death.

Neurodegeneration. Neurodegenerative disorders present a major public health challenge. This initiative will provide new or expanded funding in various areas, including: identification of disease genes and heritable risk factors; the causes and pathogenesis of neurodegeneration; improved animal models; research

leading to clinical trials of novel therapeutics; and, improvements in and access to brain imaging for early detection and application of protein and DNA array technologies.

Auditory Cell Development and Regeneration. In humans, the loss of auditory sensory cells (hair cells) is a common event leading to deafness and hearing impairment. This initiative will focus on obtaining a better understanding of the molecular mechanisms governing hair cell development, which may provide important clues about the pathways leading to hair cell regeneration.

Identification of Genes Expressed in the Visual System. The initial phase of this expanded research initiative will focus on gene discovery to identify and sequence genes that are expressed in the visual system. The gene expression phase will involve sophisticated methods for quantifying the expression of genes in single tissues or cells. The ultimate product will be a publicly available and easily accessible catalog and collection of microarrays of all the genes expressed in human and mouse ocular tissue.

Functional Dynamics of Gene and Protein Expression in Brain Aging. The response of the aging brain to traumatic, toxic, and disease processes is controlled in large part by the patterns and timing of gene expression. This new initiative will provide critical insight into the underlying mechanisms of aging and of diseases of the nervous system. Studies will focus on delineating and comparing gene and protein expression patterns during normal and pathological aging to identify unique age-, neurodegeneration-, and disease-related profiles of molecular changes in rodent, primate, and human brains.

Model Genetic Organisms for the Study of Addiction. Much of our understanding of the genetic basis of addiction has come from the use of animal models. Previous mouse studies have identified chromosomal locations associated with sensitivity to drug responses. Additional research will focus on pinpointing important genes within these regions, as well as understanding gene-gene and gene-environment interactions related to addiction. In addition, new and better animal models will be developed that more closely model addiction and provide new ways to assess craving and relapse.

Factors That Contribute to the Time-of-onset and Severity of Hearing Impairment. New research will seek to identify genetic and/or environmental factors that modify the physical manifestation of mutations in deafness genes. This knowledge is extremely important for providing accurate assessments of severity and progression of disease.

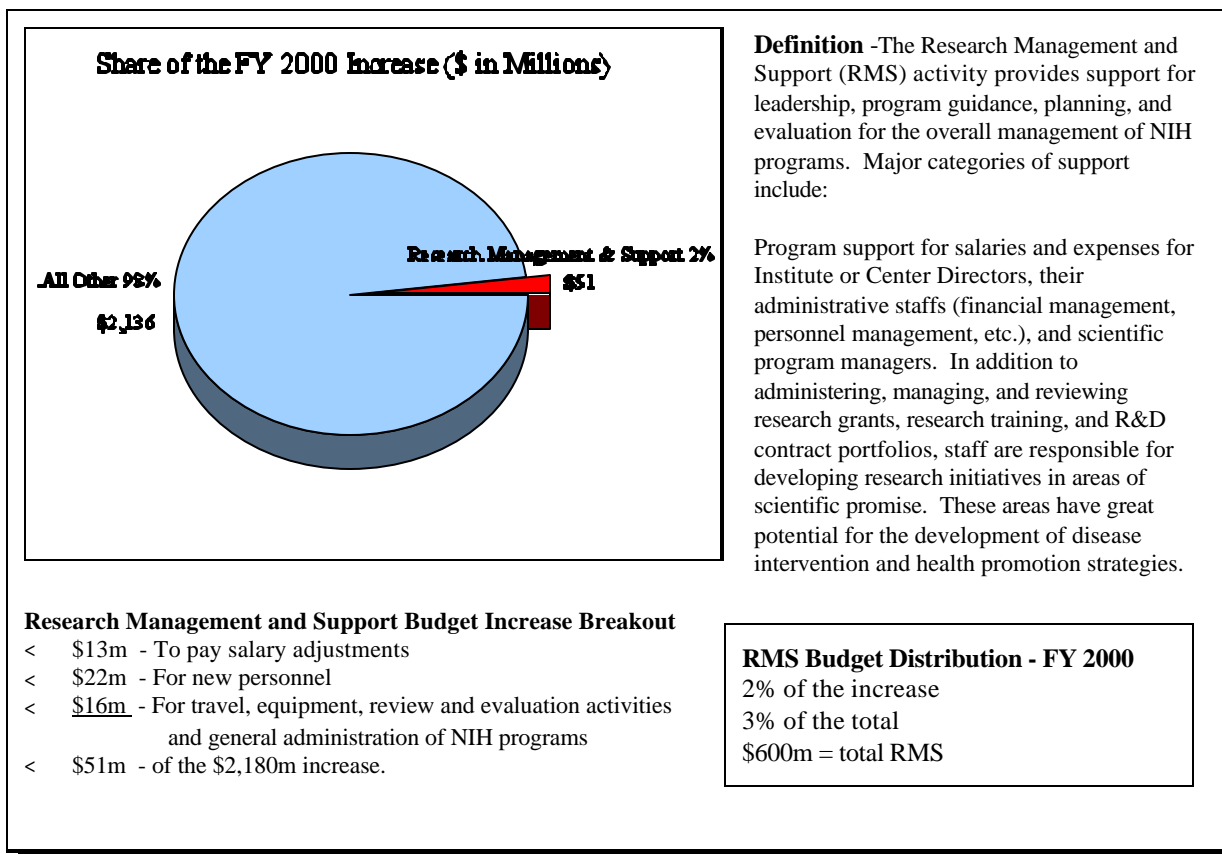
Toxicological Testing on Herbal Dietary Supplements. Over one-third of U.S. adults use herbal medicines or herbal products. Of the nearly 2000 herbal products in use, only a few have been adequately tested for efficacy and toxicity. A new research program will characterize potential adverse health effects, including reproductive toxicity, neurotoxicity, and immunotoxicity, as well as those effects associated with acute high dose exposure and chronic exposure to lower doses. Special attention will be given to the potential for herb/herb and herb/drug interactions and the responses of sensitive subpopulations such as pregnant women, children, the developing fetus, and the elderly. Initial studies will focus on goldenseal, comfrey, ginkgo biloba, echinacea, berberine, pulegone, aloe vera, ginseng, kava kava, and milk thistle extract.

Development of Neuroimaging Biomarkers for CNS Disorders. Neuroimaging of disease-related biomarkers is beginning to be used in clinical trials to assess the efficacy of experimental therapies for CNS disorders. A major limitation, however, has been the paucity of radiotracers (imaging agents) for CNS

receptors and other signaling molecules. This new research program will focus on the development and application of imaging biomarkers in studies of the course and treatment of CNS disorders.

Linking Basic Genetic Data to Mental Health. This new research initiative will begin to make connections between findings from model systems and human neural processes that go awry in complex mental health disorders. For example, dysfunctional circadian systems are central to emotional and cognitive disturbances. A major area of discovery will involve linking the molecular genetics of the circadian clock system in the mouse with similar genes in humans to understand the impact of altered clock genes and clock gene expression for human health and well-being.

RESEARCH MANAGEMENT AND SUPPORT (RMS)



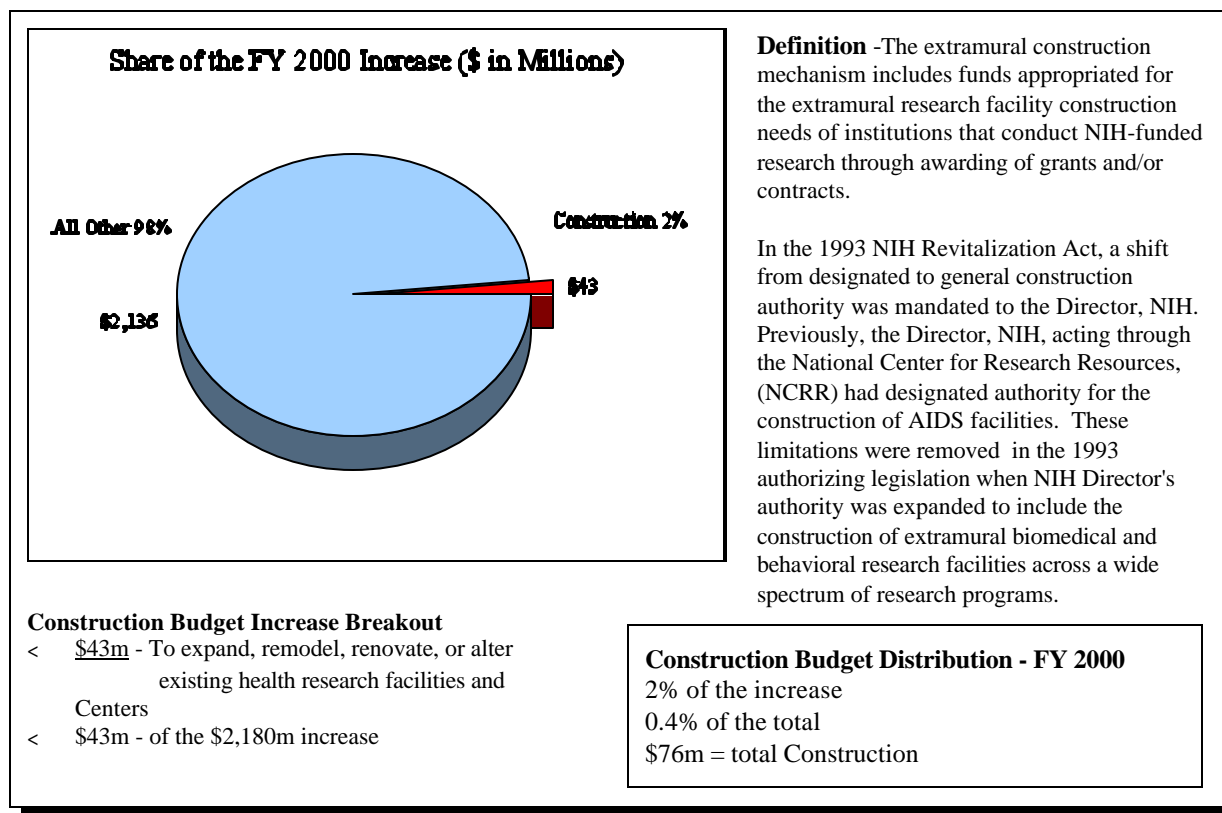
Selected FY 2000 RMS Programs

Toxicology and Environmental Outreach to Disadvantaged Communities. Because of where they live, many minority citizens are at increased risk from environmental and occupational hazards. NIH will expand an ongoing program in which faculty at Historically Black Universities and Colleges (HBCUs) train health professionals, community leaders, and other minorities to search NIH databases for hazardous waste information, and to use the results to improve the health of local citizens. The pilot program was very successful, and now the effort will be expanded from the HBCUs to include, directly, members of minority and socioeconomically depressed communities.

Guide and Monitor Extramural and Intramural Research Activities of the ICs. These activities include development of: scientific programs and guidance to help ensure that the best scientific opportunities and public health needs are met; health information programs for the public and health professionals; technology transfer activities to speed the translation of research to the private sector; and administrative activities to ensure proper stewardship of public resources. RMS will also be used for support services for prevention programs, education initiatives, enhanced information technology infrastructure; coordination of

trans-NIH efforts in autoimmune diseases, bioterrorism, and other trans-NIH issues; and scientific workshops and site visits.

CONSTRUCTION



Selected Construction Programs

Neuroscience Facilities. New funds will be used for the construction of research and training facilities for neuroscience research, including the pathogenesis of sensory age-related decline; substance abuse research; and research in biological, cognitive, and social psychology. A 3-Tesla functional Magnetic Resonance Imaging Center for brain research will be constructed.

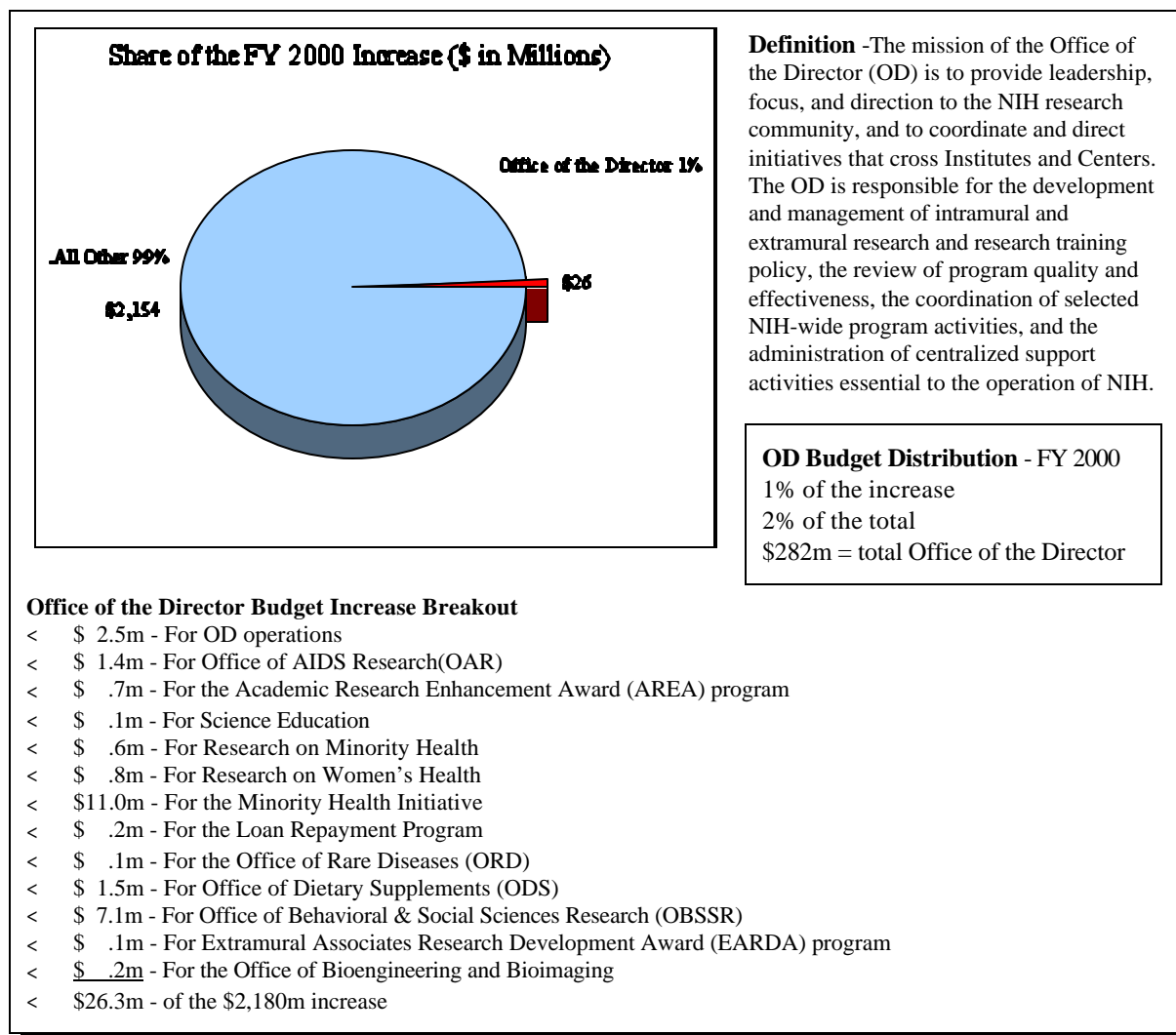
Good Manufacturing Practice Facilities. New funds will be used to construct shared resources for Good Manufacturing Practice cellular therapy, gene transfer, gene discovery, molecular genetics, genetic epidemiology, and computational biology to develop novel approaches to treat malignancies, infectious diseases, pediatric heritable diseases, etc.

Animal Facilities. New animal facilities for transgenic and gene-targeted mouse models of human disease to advance research and to ensure protection from pathogens and other biohazards will be constructed.

Medicinal Chemistry Research Facilities. New medicinal chemistry research facilities and antibody engineering laboratories will be constructed. Their purpose is the discovery, design, and synthesis of new drugs, monoclonal antibodies, immunoconjugates, and related derivatives in support of clinical trials for

unmet therapeutic needs in human health. Special emphasis is placed on the development of therapeutics that interrupt disease processes without toxic side effects.

OFFICE OF THE DIRECTOR (OD) ACTIVITIES



Selected FY 2000 OD Programs

Minority Health/Research Initiatives. NIH is expanding the Minority Health Initiative as part of its efforts to address health disparities. This increased emphasis reflects the central role that NIH plays in eliminating health disparities through medical research, research training, and dissemination of scientifically sound medical information.

Bioengineering Research. A new Office of Bioengineering and Bioimaging will foster new basic understanding, collaborations, and transdisciplinary initiatives among the biological, medical, physical, engineering, and computational sciences. Included will be coordination of research, training opportunities, and sponsorship of scientific symposia associated with biomedical engineering.

Behavioral and Social Sciences Research. Research will focus on understanding and improving adherence to treatment, taking into account the patient, the provider, and the context in which the treatment occurs. This initiative will also enhance the capacity of medical schools to incorporate research findings from the behavioral and social sciences into medical education, expose medical students to the social and behavioral aspects of disease, and provide a forum for the teaching of evidence-based behavioral treatment approaches.

Dietary Supplements. Databases of public-oriented information on federally funded research and scientific papers on dietary supplements are being developed or expanded. New fact sheets on vitamins and minerals and on herbs and botanicals are also being developed. Additional research will be stimulated through the conduct of conferences, workshops, and presentations at national and international meetings relevant to dietary supplements.

Academic Research Enhancement Award (AREA). The AREA Program is being expanded to enable additional students to participate in experiences related to research careers in the biomedical or behavioral sciences. AREA grants provide support for research and enhance the research environment at colleges and universities that award degrees in health-related sciences, have provided undergraduate training for a significant number of the Nation's research scientists, but have not been major recipients of NIH research grants.

Women's Health. Enhanced efforts are being made to ensure the inclusion of women and minorities in clinical research and encourage development of opportunities for the entry and advancement of women in biomedical careers. New initiatives include a pilot program of models for Centers for Women's Health Research Scholars designed to increase the number of young investigators in women's health research and facilitate multidisciplinary investigations in women's health; a focus on molecular/genetic and physiological bases for differences in health and disease between men and women; and development of programs in basic and clinical research on urologic and urogynecologic health and disease in women.